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#279

The hemorrhagic fevers, with particular reference to the hemorrhagic fever found in Korea.

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In 1951 an acute infectious disease marked by fever, severe affection of the general state of health, pains, vomiting, proteinuria and other renal symptoms as well as extensive hemorrhagic manifestations and cardiovascular disturbances, occurred among the troops of the United Nations committed to action in Korea.

After closer study this disease, new even to Korea, was identified as a malady which had occurred years ago in the basin of the Amur River and its tributaries, and which had been investigated by Russian and Japanese scientists under the designation of epidemic hemorrhagic fever or hemorrhagic nephrosis-nephritis, respectively (Mayer). It was further established that the hemorrhagic fever occurring in Korea, Manchuria and Far-Eastern Siberia belongs to a group of diseases with similar courses but etiological differences, found in various parts of Russia as well as in the north of Scandinavia (Gajdusek).

In the present paper, based on the observation of 18 cases of Far-Eastern hemorrhagic fever with fatal outcome, the epidemiology, clinical course and pathological anatomy of this "new" disease will be discussed by way of summation.

Epidemiology.

The map in Fig. 1 gives a perspective on the endemic foci of hemorrhagic fever found in the Soviet Union, Scandinavia and the Far East. A total of 6 different forms of this disease have been recognized to date, occurring in areas widely separated geographically. The clinical course allows the differentiation of 3 groups: Group I: The fever of Uzbekistan and Crimean fever, marked by profuse gastro-intestinal bleeding; Group II: The Far Eastern and the Scandinavian fever, usually accompanied by involvement of the kidney, and Group III: The fever of Omsk and the Bucovina-fever. A cross immunity apparently exists between the latter two.

Table 1 shows a few data on the pathogen, carrier, contagious reservoir, main season of occurrence, contagiosity, mortality and clinical peculiarities of these 6 hemorrhagic fevers known to date.

Viral elements have been established as pathogens in 3 of the diseases. The pathogen of Bucovina-fever probably is a virus. The pathogen of the hemorrhagic diseases occurring in the Far East and in northern Scandinavia has not yet been identified with certainty.

All maladies enumerated here are "spot diseases," i.e. their incidence is more or less local in scope. In addition, they are "search-diseases" connected with the season, generally attacking agricultural workers, foresters, hunters or soldiers on forward positions.

The vectors in 4 of these diseases are ticks, which in part also constitute the reservoir. Mites were suspected as carriers in the case of Far-Eastern fever. Rodents and other wild and domestic animals could act as reservoirs of contagion. A transmission from man to man has been seen only in the case of Uzbekistan fever. In the latter and in Far-Eastern fever the mortality is quite considerable.

The hemorrhagic tendency is present in all 6 maladies, but Crimean and Uzbekistan fever is marked by its inclination to profuse gastro-intestinal bleeding, the Far-Eastern and Scandinavian hemorrhagic fever by involvement of the kidney. Forty percent of the Omsk-fever cases have atypical pneumonia, while severe cases of Bucovina-fever are complicated by meningo-encephalitis.

The map in Fig. 2 shows the geographic dissemination of Far-Eastern fever. In Korea the disease is conspicuously limited to a relatively narrow area north of Seoul. Whether the disease is found also in North Korea and thus constitutes a connection with the endemic region on the Amur, is not known.

Just as the other hemorrhagic fevers, Korean fever is a pronounced seasonal malady with one peak in May or June and another in October or November. Isolated cases occur also in the remaining months. In the endemic zone of Korea, the infections occur either sporadically or (less frequently) in small, isolated groups of 2 to a reported maximum of 16 cases. In the case of group afflictions the chronological inception of the disease pointed to a common source of infection. Man-to-man transmissions were not observed. Epidemiological considerations ruled out food or drinking water as sources of infection (Gauld and Craig).

The pathogen has not been found to date in spite of great efforts. The disease has never been successfully transmitted to animals. Russian authors were able, in 1940, to infect humans by intravenous and intramuscular injection of the serum or urine of patients in their first 5 days of illness, filtered through the Berkefeld-N filter (TB 240). Japanese investigators produced hemorrhagic fever in man by injecting a suspension of freely caught Laelaps mites, and passed the disease from man to man by injecting serum from patients (Traub and others).

The mite Trombicula is assumed to be the vector of Korean fever, and the striped Manchurian field mouse (Apodemus agrarius), widely disseminated throughout Korea, is said to be the reservoir of contagion, but these questions are still awaiting final clarification. While in the fall of 1953 a close agreement existed between the mite index, i.e. the average number of mites per trapped Apodemus on one hand, and the number of human cases reported weekly on the other, the May-July peak of illness of the same year failed to show such a correlation.

In Korea, the disease has almost exclusively attacked soldiers of the forward battle lines. More than 2,000 cases were reported between 1951 and 1954. The morbidity was approximately equal among U.S. troops, U.N. troops and troop units of the South Korean Army (Clin. Lab. Rep.).

The clinical picture.

The hemorrhagic fever of Korea has been thoroughly examined in various quarters (Andrew, Earle, Giles and others, Hibbard, Furth, Powell, Sheedy and others).

A typical case permits differentiation of 5 stages of disease: 1. The mean incubation time of 14-21 days (7-46). 2. The invasive or febrile phase, lasting about 3-5 days. This phase usually starts suddenly with shivers and fluctuating temperatures around 40°C and is accompanied by severe malaise, pains in the head, eyes and back, nausea, vomiting, thirst, dry skin, flushed face and conjunctival injection. The febrile phase already reveals petechial bleeding in the ocular conjunctiva, the mucous membrane of the pharynx and gums as well as in the skin, particularly of the arms, axillae and the waist, as a manifestation of capillary damage, connected with hemostasis. The 3rd or hypotensive phase comes with defervescence or shortly before, lasting about 5-9 days. At this time the blood pressure frequently falls, accompanied by alarming manifestations of shock and severe acceleration of the pulse. Proteinuria, microhematuria and cylindruria set in simultaneously. The white blood count shows considerable leukocyte values (50-90,000), a leukemoid reaction and an increase in eosinophils, while the number of thrombocytes, which at times have giant forms, drops off sharply (30-80,000). The hematocrit rises without change in total protein. Patients with severe shock have a reduced volume of circulating plasma and blood. The sedimentation rate usually is not increased. A splenic tumor is present in many cases. The 4th or oliguric or anuric stage (9th-13th day) follows, with reduced urine and insufficient concentration. At the same time the residual nitrogen increases and one fourth of the cases reveal moderate hypertonia. A peculiar syndrome may now develop clinically, with nausea, vomiting, confusion, stupor, hallucination, tremor and unrest. This condition may be attributed partly to uremia, partly to the relative hypervolemia.

Frequently this stage is marked by acute pulmonary edema. In serious cases there is hyperkalemia and hyperphosphatemia, as well as reduced values of serum chlorine, sodium and calcium. At the same time increased hemorrhages may occur in the skin and mucous membranes, as well as bleeding from the gastro-intestinal tract, the lungs and with the urine. Occasionally hemorrhages are observed in the central nervous system. The last stage is the diuretic phase (13th-21st day) with excessive volumes of urine and abatement of residual nitrogen. The concentrative ability of the kidneys may remain impaired for weeks or months. A restitutio ad integrum usually follows.

There are deviations from this typical course. In light cases the hypotensive and oliguric phases may be altogether absent. It is probable that inapparent infections may also occur.

Therapy.

The therapy of hemorrhagic fever to date has been purely symptomatic and places heavy demands on the physician, the nursing staff and the laboratory. Hitherto known chemotherapeutic or antibiotic agents are ineffective and are indicated only for the control of secondary bacterial infections. Even hormone therapy — particularly with cortisone or ACTH — or treatment with antihistamines fails to yield decisive results. Quite essential are early and complete bedrest, a low-salt diet rich in carbohydrates and limited fluid intake. Mild sedation is indicated from the start. If severe vomiting is present, a 5% dextrose solution is given intravenously and possibly even a salt solution, but both excessive fluid instillation with resultant formation of edema and dehydration must be avoided. In the hypotensive phase the early dispensing of Nor-Adrenalin by constant drop instillation through a horizontal catheter into the Vena femoralis has proved to be most beneficial. If considerable shock and high hematocrit values (above 55-60%) are present, prescription of low-salt human albumin is indicated, but here, too, the danger of hypervolemia must be considered. Blood transfusions are contraindicated in the case of high hematocrit values. If pulmonary edema threatens or has already set in, blood-letting must be carried out. At times an "internal" blood-letting brought about by bandaging the arms and legs suffices. Withdrawal of liquor may be feasible in the case of confusion and convulsions. The artificial kidney may be used during retention of substances normally eliminated with the urine. Finally, in the diuretic phase, possible losses of salt and potassium must be replaced under constant measurement of electrolyte. Hyperkalemia may be controlled by intravenous instillation of dextrose and insulin. Premature physical exertion during convalescence must be strictly avoided.

Mortality.

The disease has a mortality fluctuating between 5 and 15%. About one third of the fatal cases are due to primary shock. An additional portion dies of pulmonary edema. A number of patients succumb in the diuretic phase with its thoroughgoing disruptions in the water and electrolyte balance. Profuse bleeding is a less frequent cause of death. The extreme weakness caused by the involvement of the anterior lobe of the hypophysis frequently makes coughing impossible, so that aspiration pneumonia is often produced, leading to death.

Pathological anatomy.

From the pathologic-anatomical viewpoint, hemorrhages found in the skin, the mucous membranes and nearly all organs, attributable to general capillary damage, occupy the foreground. The triad of hemorrhages into the anterior hypophyseal lobe, the renal medulla and the endocardium of

the right auricle. Extensive gelatinous edema with the albumin content of blood plasma is found in the retroperitoneal, mesenteric and mediastinal tissue in cases dying in primary shock. The kidneys are enlarged, their capsules are swollen, the medullary pyramids are sharply delineated due to congestion. There are hemorrhages in the medulla. The tubuli show signs of more or less severe degeneration, particularly in their distal parts. The whole picture corresponds strikingly to the renal lesions in yellow fever. The enterior hypophyseal lobes are initially swollen and full of blood. Later, extravasation of blood and necrosis set in. The latter may remain local or may affect all or parts of the whole organ. Focal necroses are found also in the liver, the suprarenal capsules, the pancreas and the sceletal muscle. In some cases there are hemorrhages in the brain and the meninges.

Personal observations.

Table 2 shows a summary of 18 fatal cases of Far-Eastern hemorrhagic fever observed by us. The data include: age, day of death after commencement of the illness, duration of the febrile, the hypo- or hypertensive and oliguric or anuric phases, maximal values of serum urea and leukocytes related to the day of illness, maximal and minimal hematocrit readings with the appropriate day, deviations in the electrolyte balance and, finally, the pathologic-anatomical findings.

As the chart shows, the patients were young men aged 18-29, all of them soldiers. Three of our cases (#1-3) died on the 5th, 7th and 8th day in primary shock, #3 after 5 days of anuria. Renal insufficiency combined with bronchopneumonia and pulmonary edema was the cause of death in 10 cases (#4-9, 12, 13, 16, 18). Two of our cases (#9 and 11) had massive gastro-intestinal hemorrhages terminally. In 4 cases (#10, 14, 15, 17) a collaps was the final cause of death, following a resumption of diuresis. All of our cases were febrile, fluctuating between 2 and 8 days. In part of the cases a subsequent temperature elevation is not due to the hemorrhagic fever proper, but to a bacterial secondary infection. With the exception of one case (#5), all of our patients went through a hypotensive phase of varying duration, occasionally with a second, final or prefinal drop in blood pressure. Eight patients (#7, 9, 11, 13-16, 18) experienced a rise in blood pressure, also variable in duration. The length of the oliguric or anuric phase also fluctuated. Case #16 with anuria lasting 10 days is particularly noteworthy. Here the urea amounted to 225 mg% on the last day. The serum potassium was measured at 6.3 mAq/L. All patients had leukocytosis. The maximal values in leukocytosis are found 5-8 days after the onset of illness. Patient #9 attained the highest count with 91,000 cells on the 8th day. The majority of our patients had moderately to highly elevated hematocrit readings initially, as a manifestation of the blood's thickening (e.g. 67% in patient #14 on the 5th day). Later the blood becomes diluted with hematocrit values sometimes far below normal. All patients had hypochloremia fluctuating between 61 and 83 mAq/L. In some cases there was hyponatremia and hypocalcemia as well as hyperphosphatemia and hyperkalemia.

A considerable reduction of the alkali reserve was noted in the majority of cases. Pathologic-anatomically, all cases had multiple hemorrhages in the skin, the mucous membranes and the internal organs. The characteristic triad: Bleeding in the anterior hypophyseal lobe, the endocardium of the right auricle and the renal medulla (Fig. 3-6. See plate on page 1737) was absent only in case #11, where the hemorrhage in the right auricle was missing.

The three cases passing away early (#1-3) had considerable retroperitoneal edema. The anterior hypophyseal lobe either was permeated by hemorrhages only or revealed focal necroses. In cases #7-10 and 12, 17 and 18 the organ was almost entirely necrotic. Bronchopneumonia of varying extent was found in 9 cases. Seven cases showed focal necroses in the suprarenal capsules and, in part, in the liver.

In summary, the course as well as the autopsic findings were relatively uniform among our 18 cases; next to the multiple hemorrhages, tubular renal injury and the cessation of the anterior hypophyseal lobe's function dominated the picture.

As an example, one of the cases will be described in more detail:

S.H., 24. Admitted to the hospital on the 3rd day of illness. Patient fell ill on 13 November 1954 with an elevated temperature, shivers, aches in the head and limbs, weakness, loss of appetite, cough and thirst. At admission (16 November), face flushed with high fever, conjunctival injection and petechiae, diffuse pharyngeal erythema. RR 125/70. After an hypotensive phase on 18 November the patient became oliguric or anuric for 7 days, with rising urea concentrations. From 25 November on, excessive elimination of urine without clinical improvement. The patient became almost comatose and again febrile (bronchopneumonia). Since he was unable to cough up the bronchial mucus, a tracheotomy was carried out on 27 November. Despite treatment with cortison, albumin and Nor-Adrenalin, the state of shock reappeared on 28 November and could not be palliated. The patient died on 30 November, on the 18th day of illness. Pathologic-anatomically, there was the typical triad with hemorrhages in the anterior hypophyseal lobe, the renal medulla and the endocardium of the right auricle. The anterior lobe of the hypophysis was almost totally necrotic. The terminal cause of death was bilateral bronchopneumonia.

Tab. 1. Russian, Scandinavian and Far-Eastern Hemorrhagic fevers.

Name of disease	Pathogen	Vector	Reservoir	Season	Contagion/Mortality		Character
Hemorrhagic fever of Uzbekistan	virus	Hyalomma anatolicum	large animals (?)	June-July	∤	30%	profuse gastro-intestinal bleeding
Hemorrhagic fever of the Crimea	virus	Hyalomma marginatum	ticks, rabbits, birds(?)	June-August	∅	3%	profuse gastro-intestinal bleeding
Hemorrhagic fever of theFar East	unk.	Trombicula mites	Apodemus agrarius(?)	May-June Oct-Nov	∅	5-15%	severe renal involvement
Nephropathia epidemica of northern Scandinavia	unk.	unk.	mice (?)	winter	∅	0%	severe renal involvement
Hemorrhagic fever of Omsk	virus	Dermacentor pictus	ticks Microtus gregalis large animals(?)	May-August	∅	1-2%	40% atypical pneumonia lymphadenopathy
Hemorrhagic fever of the Bucovina	virus(?)	Ixodes ricinus	unknown	July	∅	1-2%	diffuse meningo-encephalitis, cross immunity to Omsk-fever

Nr.	Age	Day of death	Cause of death	Days of fever	Hypo-tension days	Hyper-tension days	Oliguria anuria days	Urea/mg% max/day	Leukocytes max/day	Hematocrit max day / min day	Electrolyte	Pathologic-anatomical findings
7	22	9	Renal insufficiency, pulmon. edema	3	3rd-4th, 9th	8th	7	189/9th	60,000/5th	58.5/3rd-33/8th	Hypochloremia Acidosis	Multiple hemorrhages, incl. brain. Bleeding in anterior hypophys. lobe, rt. auricular endocard., renal medulla. Total necr. of ant. hypophys. lobe. Focal necr. in supraren. capsule.
8	21	10	Renal insufficiency, pulmon. edema	4	5th-10th	Ø	5	182/10th	8,800/4th	61.5/5th-26.2/10th	Hypochloremia Acidosis	Multiple hemorrhages, also in anterior hypophys. lobe, right auricular endocardium, renal medulla. Total necr. of anterior hypophys. lobe. Necroses in supraren. caps. Pulmon. edema.
9	27	10	Renal insufficiency, gastro-intestinal bleeding	5	6th	9th	6	173/10th	91,600/8th	62/6th-31.8/10th	Hypochloremia Acidosis	Multiple hemorrhages, incl. brain. Bleeding in anterior hypophys. lobe, rt. auricular endocard., renal medulla. Total necr. of ant. hypophys. lobe. Tubular necr. Necr. esophagitis and gastritis.
10	21	10	Shock in diuretic phase, pulmonary edema	6	10th	Ø	5	186/8th	85,000/6th	54.8/5th-39/8th	Hypochloremia Hypocalcemia Acidosis	Multiple hemorrhages, also in hypophys. lobe, rt. auricular endocard., renal medulla. Total necr. of ant. hypophys. lobe. Tubular necr. Bronchopneumonia.
11	18	11	Gastro-intestinal & retroperitoneal hemorrhages	6	10th-11th	7th	-	21/9th	22,400/8th	52/8th-29/10th	-	Multiple hemorrhages, also in anterior hypophys. lobe, renal medulla. Focal necr. of ant. hypophys. lobe. Infiltration of liver & pancreas. Retroperit. bleeding.
..	..	11	Renal insufficiency, ... pneumonia	6	6th-11th	Ø	5	105/10th	39,100/8th	55/7th-45/10th	Hypochloremia	Multiple hemorrhages, also in ant. hypophys. lobe, rt. auric. endocardium, renal medulla. Total necr. of ant. hypophys. lobe. Necr. liver & kidneys. Bronchopneumonia.

Tab. 2. Findings in connection with 18 fatal cases of Far Eastern hemorrhagic fever.

Nr.	Age	Day of death	Cause of death	Days of fever	Hypo-tension days	Hyper-tension days	Oliguria anuria days	Urea/mg% max/day	Leukocytes max/day	Hematocrit max day	Hematocrit min day	Electrolyte	Pathologic-anatomical findings
1	22	5	Shock	2	3rd-5th	ø	3	53/5th	70,000/5th	53/2d	39/5th	Hyponatremia Hypochloremia	Multiple hemorrhages, also in anterior hypophys. lobe, rt. auricular endocardium, renal medulla, retroperit. edema.
2	27	7	Shock, pulmonary edema, broncho-pneumonia	5	6th-7th	ø	4	100/6th	20,800/5th	50.8/5th	-	Hyponatremia Hypochloremia	Multiple hemorrhages, also in anterior hypophys. lobe (partly necrotic), right auric. endocardium, renal medulla. Liver necrosis. Retroperitoneal edema. Bronchopneumonia.
3	19	8	Shock, commencing renal insufficiency	7	6th-8th	ø	5	100/8th	10,200/5th	68/6th	54/8th	Hypo-chloremia	Multiple hemorrhages, also in anterior hypophys. lobe, rt. auricular endocardium, renal medulla. Liver necr. Necr. suprarenal capsules. Retroperitoneal edema.
4	22	8	Renal insufficiency, auricular flutter	2	2nd	ø	7	254/8th	16,000/6th	53/4th	33.5 8th	Hypochloremia Hypocalcemia Hyperphosphat-emia	Multiple hemorrhages, also in anterior hypophys. lobe, rt. auricular endocardium, renal medulla. Bronchopneum.
5	21	8	Renal insufficiency, heart block flutter	7	ø	ø	5	161/8th	55,000/7th	62.5/6th	42/3rd	Hypochloremia Acidosis	Multiple hemorrhages, also in anterior hypophys. lobe, rt. auricular endocardium, renal medulla, necroses. Skeletal musculature.
6	26	8	Renal insufficiency, bronchopneumonia	8	4th-6th, 8th	ø	5	250/8th	36,000/5th	57.4/4th	32.5/7th	Hypochloremia Hypocalcemia	Multiple hemorrhages, also in anterior hypophys. lobe, rt. auricular endocardium, renal medulla. Partial necr. in anterior hypophys. lobe, liver and suprarен. capsules Bronchopneumonia.

Nr.	Age	Day of death	Cause of death	Days of fever	Hypo-tension days	Hyper-tension days	Oliguria anuria days	Urea/mg% max/day	Leukocytes max/day	Hematocrit max day	Hematocrit min day	Electrolyte	Pathologic-anatomical findings
13	29	13	Renal insufficiency, pulmonary edema	6	5th-8th	9th-12th	9	259/12th	57,000/7th	57/5th-	32/10th	Hypochloremia Hyperkalemia Acidosis	Multiple hemorrhages, also in ant. hypophys. lobe, right auric. endocardium, renal medulla. Focal necr. of ant. hypophys. lobe. Pulmon. edema. Bronchopneumonia
14	20	14	Shock in diuretic phase, broncho-pneumonia	5	3rd-4th	5th-6th	4	291/8th	68,000/4th	67/5th-	48/10th	Hypochloremia Hypocalcemia Acidosis	Multiple hemorrhages, also in ant. hypophys. lobe, right auric. endocardium, renal medulla. Focal necr. in suprarenals, bronchopneumonia
15	20	15	Shock in diuretic phase. Heart block bronchiolitis	4	4th-5th	6th-8th	4	239/13th	34,100/6th	61.5/6th-	41/11th	Hypochloremia Acidosis	Multiple hemorrhages, also in ant. hypophys. lobe, right auric. endocardium, renal medulla. Focal necr. of ant. hypophys. lobe. Bronchiolitis
16	20	15	Renal insufficiency, hyperkalemia	6	5th-6th	7th-14th	10	225/15th	10,100/5th	57.8/8th-	32.5/10th	Hypochloremia Hyperkalemia Acidosis	Multiple hemorrhages, also in ant. hypophys. lobe, right auric. endocardium, renal medulla. Focal necr. of ant. hypophys. lobe & suprarenals. Slight retroperitoneal edema
17	24	19	Shock in diuretic phase, broncho-pneumonia	7	7th, 17th	ø	7	202/19th	65,900/8th	57/7th-	39/19th	Hypochloremia Hyponatremia Hyperphos-phatemia Acidosis	Multiple hemorrhages, also in ant. hypophys. lobe, right auric. endocardium, renal medulla. Total necr. of ant. hypophys. lobe. Slight retroperit. edema. Bronchopneumonia
18	27	20	Renal insufficiency, bronchopneumonia	6		20th	8th-11th	6	218/10th	26,200/8th	- 35.5/8th	Hypochloremia Acidosis	Multiple hemorrhages, also in ant. hypophys. lobe, right auric. endocardium, renal medulla. Total necr. of ant. hypophys. lobe, Necrotizing bronchopneumonia